NIEHS News

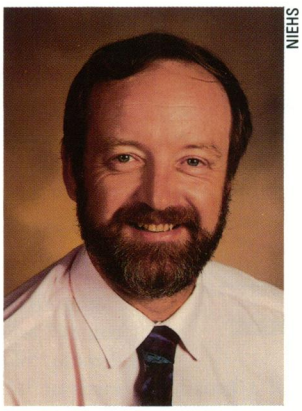
Strengthening the Foundation of Risk Assessment

The growing controversy over the risk assessment policies of U.S. regulatory agencies is emotional and divisive. At the root of the problem is the huge magnitude of uncertainty that often accompanies risk estimates for a given exposure level of an environmental agent. This uncertainty is created by weaknesses and/or inadequacies in the available scientific data and the difficulties in translating biological information into mathematics. Reliance on default assumptions that are open to legitimate criticisms fuels the controversy. Regulatory agencies are often the victims in risk assessment wars because they must make regulatory decisions whether or not appropriate scientific information is available and ensure that these decisions protect the public from adverse health effects.

NIEHS has a long record of accomplishment, through both extramural and intramural programs, on the mechanisms whereby chemicals cause disease and on the relationship between chemical exposure and adverse health outcomes in humans. The National Toxicology Program, the nation's most comprehensive toxicity testing program, is centered at NIEHS and has contributed substantially to the hazard identification component of risk assessment. The major goals of NIEHS in risk assessment are 1) to strengthen the scientific foundation on which risk assessments are based by increased understanding of mechanisms and dose–response relationships, the identification of sensitive subpopulations, and evaluation of the relevance of animal models for estimating human risks; 2) to develop novel and more reliable approaches to estimate human risks; 3) to collaborate with regulatory agencies on conducting risk assessments; and 4) to communicate findings to the public in an understandable and objective way.

Laboratory of Biochemical Risk Analysis

Although many components of NIEHS conduct research that is directly relevant to various aspects of risk assessment, the Laboratory of Biochemical Risk Analysis (LBRA) has served as the focus for the development and application of laboratory approaches relevant to risk assessment. George Lucier has been chief of LBRA since its inception in 1984. Many notable contributions have been made by LBRA scientists, but the most visible is research on dioxins, genetic susceptibility, and biomarkers. The work on dioxin has addressed dose–response relationships and comparison of human and rodent responses. The dose–response studies have demonstrated that the response to different levels of exposure to dioxin cannot be predicted solely on the basis that the response is receptor mediated. It is generally accepted that most, if not all, of dioxin's effects require interaction with a cellular protein called the Ah receptor. The Ah receptor appears to function like receptors for steroid hormones. In a series of papers by Lucier and coworkers Angelika Tritscher, Charles Sewall, Jack VandenHeuvel, and George Clark, evidence was presented that the amount of dioxin required to activate cellular enzymes and affect growth factors is linearly related to concentrations of dioxins in certain body tissues. It is also clear that ovarian hormones, probably estrogens, are necessary for dioxin-mediated liver cancer; the model dioxin, 2,3,7,8-tetrachloro-*p*-dioxin (TCDD), promotes liver tumors in intact rats but not in rats from which the ovaries have been removed.



NIEHS

George Clark—researching sensitivity to dioxins

In contrast to data on the activation of cellular enzymes, TCDD's effects on proliferation of liver cells and growth of existing cancer cells are not strictly proportional to the dose of TCDD. Much of the dose–response work has been conducted on liver, but the NIEHS work has recently demonstrated that the mechanism responsible for TCDD-mediated lung cancer is different from that for liver cancer; ovarian hormones are necessary for liver cancer but protect against lung cancer. This finding is especially relevant in light of several studies which demonstrated that dioxin exposure in the workplace is associated with increased risk of respiratory tumors.

LBRA scientists are now attempting to characterize the factors that control dose–response relationships for different effects mediated by the Ah receptor. LBRA molecular dosimetry studies are now using sensitive methods such as reverse-transcriptase polymerase chain reaction to detect dioxin-mediated changes in gene expression for exposure levels encountered by the overall population.

One of the important questions concerning risk assessment for dioxins is the sensitivity of humans to these compounds. This issue is being addressed by a large multilaboratory collaborative study that includes George Clark and Angelika Tritscher of LBRA, Neil Caporaso of the National Cancer Institute, Larry Needham of CDC; Maria Teresa Landi and Pier Bertazzi of the University of Milan, Paolo Mocarelli and Paolo Brambilla of Desio Hospital, Detlev Jung of the University of Mainz, Lutz Edler of the University of Heidelburg, George Lambert of Loyola University, Oliver Hankinson of the University of California-Los Angeles, and Linda Birnbaum and Dagmar Lang of EPA. One goal of the study is to identify human genetic markers for susceptibility to the toxic and carcinogenic effects of dioxins. By characterizing the receptor and the changes in gene expression, markers may be identified that correlate with adverse human health effects.

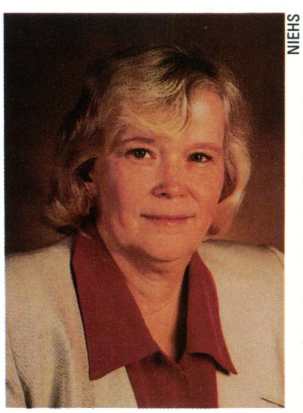
For this study, two cohorts of people exposed to high concentrations of dioxins have been assembled. One of the cohorts is from Seveso, Italy and was exposed to high levels of dioxins after a chemical plant explosion in 1976. The second cohort includes workers exposed occupationally at a chemical plant synthesizing 2,4,5-trichlorophenol and other chemicals contaminated with dioxins. Within these cohorts certain individuals developed chloracne, a skin lesion that is a response to dioxin exposure, whereas others exposed to similar concentrations did not develop chloracne. Analyzing the genetic and biochemical differences in these people and correlating the results to other health effects should provide insight into the sensitivity of humans to dioxins. LBRA scientists are working closely with NIEHS's new Laboratory of Quantitative and Computational Biology to develop dose–response models for the cancer and noncancer effects of dioxins, described later in this section.

Douglas A. Bell is carrying out studies on human genetic susceptibility to cancer-causing agents. Inherited variability in the ability to detoxify carcinogens has been associated with increased cancer susceptibility. Presumably, individuals who carry high-risk genotypes suffer more genetic damage as a result of chemical exposure, and this damage translates into greater risk of developing cancer.

NIEHS investigators have developed sensitive assays to detect susceptibility to carcinogens in cigarette smoke, foods, industrial by-products, and environmental pollution. Based on tests of more than 1000 individuals for these susceptibility genes, the frequency of the at-risk genotypes vary significantly among Asians, Caucasians, and African-Americans. Such variation suggests that some of the differences in cancer incidence among ethnic groups may be due to genetic differences as well as exposure differences.

In collaboration with Jack Taylor of the NIEHS Epidemiology Branch, LBRA is testing the effect of certain cancer susceptibility genes in studies of bladder cancer, lung cancer, and liver cancer. Individuals who carry the at-risk genotype for glutathione transferase μ, an enzyme that detoxifies constituents of cigarette smoke, suffer a 70% increased risk of bladder cancer. In ongoing studies with researchers at the National Cancer Institute, Columbia University, University of North Carolina, and University of Keele, England, NIEHS is exploring how genetic variability in the metabolism of carcinogens affects risk for cancer of the bladder, lung, liver, stomach, colon, head, and neck.

The cytochrome P450 enzymes catalyze the oxidation of drugs, carcinogens, and other xenobiotics. Joyce Goldstein's group in LBRA is looking for genetic defects in these enzymes that affect the ability of humans to metabolize chemical agents. Population studies have shown that some people are poor metabolizers of the drug *S*-mephenytoin, and defective metabolism is inherited. Metabolism of other drugs, including barbiturates, the antimalarials, and the antiulcer drug omeprazole, may be mediated by the same enzyme. Goldstein's group has isolated two new genes in the P450 subfamily. These studies use conventional cloning techniques and polymerase chain reaction to identify genetic differences in genes from poor or extensive metabolizers of the drugs. The ability of proteins coded by these genes to metabolize drugs and chemicals is being studied by Burhan Ghanayem of LBRA.

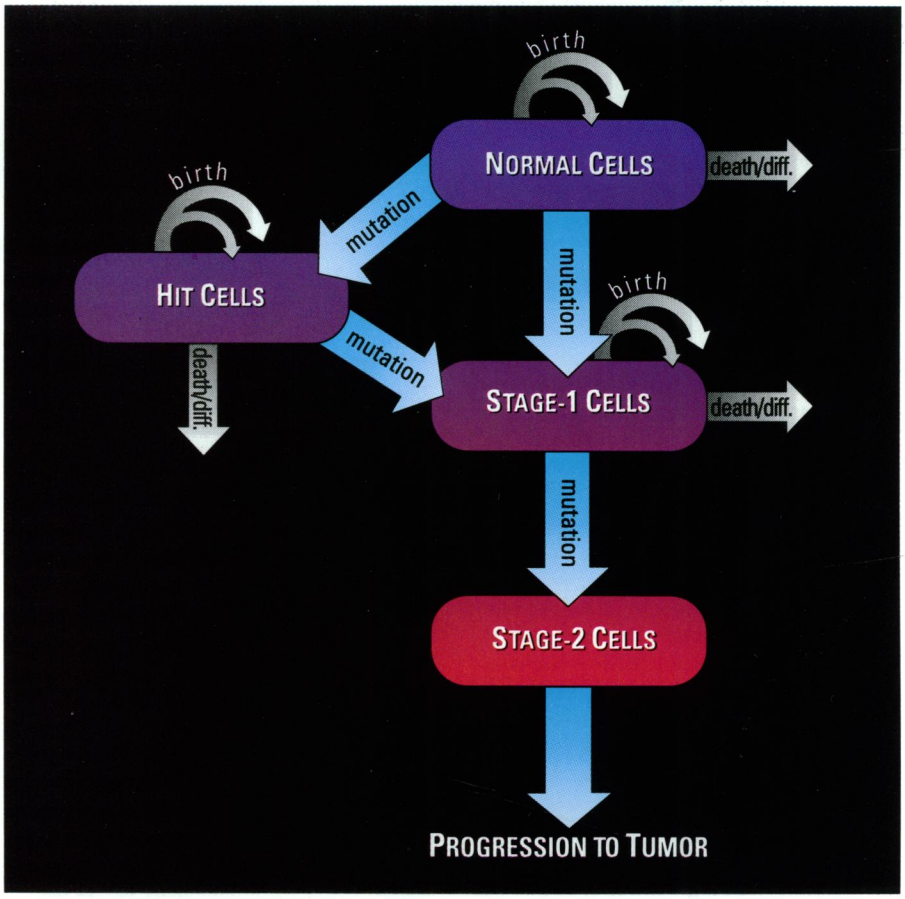


NIEHS

Joyce Goldstein—isolating P450 genes

Laboratory of Quantitative and Computational Biology

High-speed computing, the improved ability to collect a broad range of data at the biochemical and molecular levels, and recent advances in mathematics and statistics have significantly enhanced the utility of mathematical modeling in describing and studying environmental risks. The emergence of these new technologies requires a multidisciplinary approach in the quantitative sciences and creates the need for research teams in quantitative and computational areas. To address this need, NIEHS is creating a new laboratory, the Laboratory of Quantitative and Computational Biology (LQCB). The primary responsibility of LQCB is to investigate the application of mathematics, statistics, computational chemistry, electrical engineering, and computer science to the understanding of human health risks from exposure to environmental agents. LQCB will initially combine scientists from three research groups at NIEHS: a group developing new methodology and applying existing methodology to the application of quantum and statistical mechanics in environmental health, a group focusing on research in mathematical modeling aimed at developing new methodologies for risk estimation, and the NIEHS Scientific Computing Laboratory, whose primary purpose is computational support and direction for intramural research at NIEHS. In addition to these scientists, the LQCB plans to add expertise in a variety of related fields, including artificial intelligence and virtual reality. LQCB will be able to model biological mechanisms at all levels of complexity from molecular to demographic. The collaboration of LQCB and other NIEHS branches will lead to more efficient use of NIEHS resources through improved experimental design and the formal use of data from multiple sources. Current research and short-term research plans for the LQCB can be divided into seven broad areas: carcinogenic modeling, molecular modeling, biochemical and pharmacological modeling, modeling noncarcinogenic endpoints, computer science, artificial intelligence, and risk communication. Christopher Portier will be acting chief of this new laboratory.



A clonal two-path/two-stage model of carcinogenesis is being developed by members of the LQCB.

Challenging a Dioxin Hypothesis

Dioxin is believed by many to be one of the most potent carcinogens in the environment. Emerging information at the molecular level concerning the mechanism of